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 APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A  
 FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/144,106

FILING DATE: July 16, 1999

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## PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c).

JC58 U.S. PTO  
60/144106  
07/16/99

### INVENTOR(S)

Given Name (first and middle if any)	Family Name or Surname	Residence (City and either State or Foreign Country)
Marion	de Jong	The Netherlands

Additional inventors are being named on the \_\_\_\_\_ separately numbered sheets attached hereto

### TITLE OF THE INVENTION (280 characters max)

COMBINATION OF LYSINE AND ARGININE FOR REDUCTION OF KIDNEY  
UPTAKE OF PHARMACEUTICALS

### CORRESPONDENCE ADDRESS

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### ENCLOSED APPLICATION PARTS (check all that apply)

Specification Number of Pages

1

Small Entity Statement

Drawing(s) Number of Sheets

Other (specify)

### METHOD OF PAYMENT OF FILING FEES FOR THIS PROVISIONAL APPLICATION FOR PATENT (check one)

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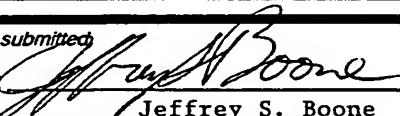
The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

No.

Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted

SIGNATURE



TYPED or PRINTED NAME

Jeffrey S. Boone

Date

7/16/99

REGISTRATION NO.

29,284

(if appropriate)

Docket Number:

1406 P

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314 654-8955

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This collection of information is required by 37 CFR 1.51. The information is used by the public to file (and by the PTO to process) a provisional application. Confidentiality is governed by 35 U.S.C. 122 and 37 CFR 1.14. This collection is estimated to take 8 hours to complete, including gathering, preparing, and submitting the complete provisional application to the PTO. Time will vary depending upon the individual case. Any comments on the amount of time you require to complete this form and/or suggestions for reducing this burden should be sent to the Chief Information Officer, U.S. Patent and Trademark Office, U.S. Department of Commerce, Washington, D.C., 20231. DO NOT SEND FEES OR COMPLETED FORMS TO THIS ADDRESS. SEND TO: Box Provisional Application, Assistant Commissioner for Patents, Washington, D.C., 20231.

1406 - P

1. Title of the invention : Combination of lysine and arginine for reduction of kidney reuptake of pharmaceuticals.
2. Brief Description of the Invention : Radio(metal)labeled peptides (and also monoclonal fragments and other compounds like certain antibiotics) undergo undesired renal reuptake and cellular retention, leading to a high kidney dose. Reduction of this re-uptake is possible using positively charged amino acids, L- and D-lysine being twice more effective than L-arginine in rat studies. In humans L-lysine was effective but at high doses it caused hyperkalemia in a number of patients. We found that the combination of L-lysine and L-arginine is significantly more effective at equimolar concentrations in reduction of kidney reuptake than both compounds alone.
3. Purpose of the Invention : To reduce kidney uptake of radiolabeled pharmaceuticals with such low doses of the combination of lysine and arginine (either in the L- or D- form) that the desired reduction of kidney uptake is achieved but hyperkalemia is prevented.
4. Detailed Description of the Invention : Radio(metal)labeled peptides (and also monoclonal fragments) undergo significant renal reuptake and cellular retention reducing the detection sensitivity of perirenal tumors and increasing kidney radiotoxicity during radionuclide therapy. We could reduce reuptake of the radiocompounds in the rat kidney *in vivo*: the most pronounced effects (50% inhibition of total kidney uptake) were obtained by D- and L-lysine (max effect achieved using 400 mg/kg). L-arginine gave a reduction of 20-30% at an equimolar dose. In human studies 15, 21 and 40% reduction of kidney uptake of [<sup>111</sup>In-DTPA]<sup>6</sup>Octreotide was reached using a dose of 25, 50 and 75 g L-lysine, respectively. The doses of 25 and 50 g L-lysine were well tolerated without any toxicity noted. However, the 75 g L-lysine dose was associated with hyperkalemia in 60% of the patients, which may result in cardiotoxicity.
5. We have found that the combination of L-lysine and L-arginine is more effective for reduction of kidney reuptake in rats than both compounds alone at equimolar concentrations. Using this combination, lower doses of the two amino acids can therefore effectively inhibit the (radio)pharmaceutical kidney reuptake and prevent hyperkalemia and cardiotoxicity.
6. Known References: 1) De Jong M, Rolleman EJ, Bernard BF, Visser TJ, Breeman WAP, Krenning EP. Inhibition of renal uptake of Indium-111-octreotide *in vivo*. J Nucl Med 37(8):1388-1392, 1996. 2) Bernard HF, Krenning EP, Breeman WAP, Rolleman EJ, Bakker WH, Visser TJ, Macke HR, De Jong M. D-lysine reduction of <sup>111</sup>In Octreotide and <sup>90</sup>Y Octreotide renal uptake. J Nucl Med 38:1929-1933, 1997.

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